

Appl. No.: 10/578,962
Amdt. dated February 16, 2010
Reply to Office Action of August 19, 2009

REMARKS/ARGUMENTS

The Objection to the Specification Should Be Withdrawn

The specification has been objected to for having embedded hyperlinks and/or other form of browser-executable code on pages 21, 33, and 38.

The specification has been amended to delete the embedded hyperlinks and/or other form of browser-executable code. Where appropriate, Applicants have further amended the specification on each of these pages to insert a citation to a journal article or the name of the linked program in replacement of the embedded hyperlink and/or other form of browser-executable code. Each of the cited journal articles can be found at a linked website and describes the program that was disclosed in Applicants' original specification. Accordingly, these amendments to the specification do not introduce new matter.

In addition to the above amendments to the specification, Applicants have amended the specification to insert a missing indefinite article (–a–) in last sentence of the first paragraph that begins on page 21 of the specification. This amendment to the specification is purely formal in nature and thus, does not introduce new matter.

In view of the amendments to the specification and the above remarks, Applicants submit that the objection to the specification should be withdrawn.

Status of the claims

Claims 36-38, 44, and 45 stand rejected, and claims 1-35, 39-43, 46-55, and 57 are withdrawn. Claim 56 was previously cancelled.

Applicants have amended claim 36 to add in part (i) the recitation, --coding for an RNA-dependent RNA polymerase and-- immediately after “said sequences”. Applicants have further amended claim 36 to recite that the sequences for replicon function “comprise at or within A/U-

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rich localities of said sequences for replicon function the insertion of one or more nuclear introns, whereby A/U-rich localities are sequence stretches of at least 20 nucleotides in length with at least 55% A/U-content or sequence stretches of 6-19 nucleotides in a row of purely A/U-containing sequences.” Support for the amendment of claim 36 can be found in original claim 44 and in the specification, particularly in the last two lines on page 6, the last two lines on page 7, lines 9-11 on page 9, and lines 7-10 on page 22.

Claims 44 and 45 have been cancelled without prejudice or disclaimer due to the amendment of claim 36 described above.

Claims 1-43, 46-55, and 57 are pending. Claims 36-38 are under examination. Claims 1-35, 39-43, 46-55, and 57 are withdrawn are withdrawn.

Reexamination and reconsideration of the application as amended are respectfully requested in view of the following remarks.

The Rejection of the Claims Under 35 U.S.C. § 112, Second Paragraph, Should Be Withdrawn

Claims 36-38 and 44-45 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as their invention. Claim 36 has been amended. Claims 44-45 have been cancelled. This rejection is respectfully traversed.

The Office Action indicates that in claim 36 the recitation of “function-conservative differences” renders this claim indefinite because it is unclear what is considered to be “function-conservative differences.”

Applicants respectfully disagree with this position of the Office because Applicants earnestly believe that one of ordinary skill in the art would understand what Applicants intend by the recitation of “function-conservative differences” in claim 36 and thus, would not find claim

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36 to be indefinite. In the interest of expediting prosecution of the instant application and not to limit the scope of their claimed invention, Applicants have amended claim 36 without prejudice or disclaimer to omit the recitation of “function-conservative” differences”.

The Office Action indicates that claim 44 is indefinite for the recitation of “capable of forming nuclear introns near or within A/U-rich localities of said sequences for replicon function”. The rejection is now moot due to the cancellation of claim 44.

In view of the amendments and remarks, the rejections of claims 36-38 under 35 U.S.C. § 112, second paragraph, should be withdrawn.

The Rejection of the Claims Under 35 U.S.C. § 102(e) Should Be Withdrawn

Claims 36-38 have been rejected under 35 U.S.C. § 102(e) as being anticipated by Klimyuk *et al.* (U.S. Patent Pub. No. 2004/0255347). Claim 36 has been amended. This rejection is respectfully traversed.

The Office Action indicates that Klimyuk *et al.* teaches a process for expressing one gene of interest from a viral vector assembled from two CrTMV based provectors through site-specific recombination, delivery of viral vector constructs by *Agrobacterium tumefaciens* infiltration, transient expressing, and that the process allows for a higher efficiency of gene expression when compared to conventional system by reducing size the size. The Office Action asserts that, because the recitation of “function-conservative differences” is indefinite and interpreted as any difference that causes increased viral replication, the reference teaches all of the limitations set forth in the instant claims.

As discussed above, Applicants have amended claim 36 to omit the recitation, “function-conservative differences”. Furthermore, Applicants have amended claim to include certain limitations of claim 44, which is not included in this rejection. As amended, claim 36 is not anticipated by Klimyuk *et al.*

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In view of the amendment of claim 36 and the above remarks, it is submitted that the rejection of the claims under 35 U.S.C. § 102 should be withdrawn.

The Rejection of the Claims Under 35 U.S.C. § 103(a) Should Be Withdrawn

Claims 36-38 and 44-45 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Klimyuk *et al.* (U.S. Patent Pub. No. 2004/0255347) in view of Rose ((2002) *RNA* 8:1444-1453). Claim 36 has been amended. Claims 44-45 have been cancelled. This rejection is respectfully traversed.

The Office Action alleges that, given the recognition of those of ordinary skill in the art of expressing a gene of interest as taught by Klimyuk *et al.*, it would have been obvious to a person having ordinary skill in the art to generate an expression vector of Klimyuk *et al.* by inserting the intron of Rose into the 5' region of the gene of interest resulting in Applicants' invention. The Office Action further alleges that one skilled in the art would have been motivated to do so given the teaching of Rose that insertion of a plant intron would enhance the expression of a gene of interest.

Applicants respectfully disagree with this position of the Office and do not believe that the Office has stated a *prima facie* case of obviousness. Without acquiescing to this position of the Office, Applicants have amended claim 36 to expedite examination of the instant application and not to limit the scope of their claimed invention. As amended, claim 36 is directed to a process of transiently expressing a sequence of interest in a plant, plant part, or plant cell culture that involves sequences for replicon function of said RNA replicon, wherein the sequences encode an RNA-dependent RNA polymerase and comprise, at or within A/U-rich localities of said sequences for replicon function, the insertion of one or more nuclear introns, whereby A/U-rich localities are sequence stretches of at least 20 nucleotides in length with at least 55% A/U-content or sequence stretches of 6-19 nucleotides in a row of purely A/U-containing sequences.

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As discussed in detail below, the combination of Klimyuk *et al.* and Rose does not render obvious Applicants' invention as presently claimed.

Klimyuk *et al.* describes a process of amplification and expression of a sequence of interest, wherein plant cells are provided with an RNA viral replicon derived from plant viruses. DNA encoding the RNA replicon is formed in plant cell nuclei by recombination between two (or more) DNA precursors of the RNA replicon. The RNA replicon is transcribed from a DNA precursor in nuclei and exported to the cytoplasm. Amplification of RNA viral vectors occurs in the cytoplasm where the viral replicase (RNA-dependent RNA polymerase) for replicating the RNA replicon is present.

Amended claim 36 differs from Klimyuk *et al.* by at least two features, namely in that the DNA encoding the RNA replicon has, in sequences for replicon function, the insertion of one or more nuclear introns at or within A/U-rich localities of said sequences for replicon function.

The effect of this difference is that the frequency with which RNA replicons appear in the cytoplasm is increased, resulting in an increased yield of the protein of interest expressed from the sequence of interest. As demonstrated in Examples 2 and 3, the instant invention achieves a huge increase in the number of GFP-expressing cells, leading to an increased expression of GFP. This effect was not achieved if introns were introduced at locations other than A/U-rich localities (*see, Example 6*).

The invention is not rendered obvious by the combination of Klimyuk *et al.* and Rose for the following reasons.

1. Klimyuk *et al.* is silent on the problem of increasing the frequency with which RNA replicons appear in the cytosol. Therefore, a person having ordinary skill in the art has no motivation to deal with this problem. Furthermore, the process of Klimyuk *et al.* is functional and gives good results with high expression levels, *i.e.*, expression levels that were considered high at the time when the invention of Klimyuk *et al.* was made. *See, Marillonnet (2004) Proc. Natl. Acad Sci. USA*

101:6852-57 (particularly the abstract), which is a scientific publication describing the invention disclosed in Klimyuk *et al.*, and which is submitted concurrently herewith in an Information Disclosure Statement. Therefore, when considering the process of Klimyuk *et al.*, a person having ordinary skill in the art would not be motivated to modify the process of Klimyuk *et al.* to make Applicants' invention as presently claimed.

2. From Klimyuk *et al.*, a person having ordinary skill in the art has no reason to consider Rose since Rose is silent on RNA viral plant expression systems. Notably, Rose is silent on nuclear-encoded RNA replicons. Rose relates to intron-mediated enhancement of expression in conventional non-viral transcription vectors. Notably, in transient expression experiments with conventional vectors, the low expression yield is limited to sites (e.g., leaf parts) where tissue was transformed. Since viral expression systems generally provide much higher expression yields than conventional expression systems, a person having ordinary skill in the art departing from a viral expression system such as that of Klimyuk *et al.* has no reason to consult a publication relating to conventional on-viral methods.
3. Even if a person having ordinary skill in the art knew about the intron-mediated enhancement of expression as described by Rose, the person having ordinary skill in the art would not attempt to apply the addition of an intron to the process of Klimyuk *et al.*, for the following reason. The fact that the process of Klimyuk *et al.* works, gives rise to replicating RNA replicons in the cytoplasm of plant cells and also gives substantial expression levels shows that transcribed replicons can get from cell nuclei where transcription takes place into the cytoplasm. Once in the cytoplasm, plant viral vectors replicate strongly to yield high copy numbers of viral RNA and give high expression levels of a protein of interest. In light of the replication in the cytoplasm, a person having ordinary skill in the art would not expect that any sub-optimal transport into the cytoplasm could significantly affect

the entire process of transcription in nuclei, transport into the cytoplasm, replication of the RNA replicon and protein expression, or would expect that replication in the cytoplasm makes any sup-optimal upstream steps irrelevant.

4. The process of amended claim 36 differs by at least two features from a process based on the combination of Klimyuk *et al.* and Rose, and neither of these documents contains a hint to any of these two differences. Importantly, even if Klimyuk *et al.* and Rose are combined, the feature of claim 36 “whereby said sequences for replicon function exhibit at localities of high A/U content . . .” is not obtained and is not taught or even suggested by the combination of the cited documents. Accordingly, the combination of Klimyuk *et al.* and Rose does render obvious to the subject matter defined by amended claim 36.
5. Furthermore, it is even counter-intuitive for a person having ordinary skill in the art to consider optimization of the sequences for replicon function of a DNA-encoded RNA replicon. Rose considers expression in a plant of a gene foreign to the plant host such as GUS. Foreign non-plant genes cannot generally be considered to be optimised for expression in plants. Thus, optimization may be tried. In contrast, in viral expression systems, viral vectors are typically used that are optimized by evolution for plant hosts. Thus, from the cited documents, there is no reason or motivation that would lead a person to having ordinary skill in the art to consider optimization of the sequences for replicon function of a plant viral vector.

For the reasons stated above, Applicants submit that the Examiner has not made a *prima facie* case of obviousness against the amended claims. In view of the amendments and remarks, Applicants respectfully request that the rejections of the claims under 35 U.S.C. § 103(a) be withdrawn.

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CONCLUSION

In view of the above amendments and remarks, Applicants submit that the rejections of the claims under 35 U.S.C. §§ 102(e), 103(a), and 112, second paragraph, are overcome. Applicants respectfully submit that this application is now in condition for allowance. Early notice to this effect is solicited.

If in the opinion of the Examiner a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefor (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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